REMARKS

Claims 1-4 and 9 are currently pending in the application. Claims 1 and 9 are amended. The amendments find support in the specification and are discussed in the relevant sections below. No new matter is added.

Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1-4 and 9 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Office Action states that claim 1 is indefinite in the recitation "comprising a non-Goodpasture fragment of α3(IV) NC1 domain and comprising amino acid residues 185-203 of SEQ ID NO:10," because it is unclear whether the composition comprises one or two fragments of α3(IV) NC1 domain (page 2, lines 19-22). In response, Applicant has amended claim 1 to clarify that the composition comprises a non-Goodpasture fragment having the recited amino acid sequence, thereby obviating the rejection.

The Office Action further states that claim 9 is indefinite in the recitation of "amino acid residue 245 of SEQ ID NO:10," because SEQ ID NO:10 has only 244 amino acid residues (page 2, lines 23-24). Applicant thanks the Examiner for pointing out this error, which was inadvertently entered in an Amendment dated September 11, 2002, and has amended the claim to properly recite amino acid residue "244." This amendment is supported by the specification as filed (see, e.g., Table 1), and does not represent new matter.

Applicant believes that the above-discussed amendments to claims 1 and 9 obviate the rejections under 35 U.S.C. § 112, second paragraph, and respectfully requests reconsideration and withdrawal of the rejections.

Claim Rejections Under 35 U.S.C. § 112, First Paragraph

Claim 9 is rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor, at the time the application was filed, had possession of the claimed invention. This is a new matter rejection, as the Examiner states that specification as originally

filed does not provide support for the phrase "amino acid residue 180 to amino acid residue 245 of SEQ ID NO:10." Applicant has amended claim 9 to properly recite "amino acid residue 181 to amino acid residue 244 of SEQ ID:10," which is supported by the original specification (see, e.g., Table 1) , thereby obviating the rejection.

Claims 1-4 and 9 are rejected under 35 U.S.C. § 112, first paragraph, because the specification disclosure allegedly does not enable one skilled in the art to practice the invention without an undue amount of experimentation. Applicant respectfully traverses this rejection.

The Examiner states that "the terms 'comprising' and 'having' are open ended and extend the fragment of α3(IV) NC1 peptide to include additional unrecited amino acids." The Examiner further states that:

> ***minor structural differences*** among structurally related compounds or compositions can result in substantially different biological activities. Because of the lack of sufficient guidance and predictability in determining which ***modifications*** would lead to the inhibition of melanoma cells or αvβ3 binding and that ***the relationship between the fragment and its activity was not well understood.*** It would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of claimed fragments of α3(IV) NC1. Without sufficient guidance, the ***changes*** which can be made in the structure of "fragments" and still provide inhibition of melanoma cell proliferation or αvβ3 binding ability is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. (Office Action page 3, line 35, through page 4, line 7; emphasis added.)

Although the Examiner is correct that the terms "comprising" and "having" are open ended and can include additional residues, all of the claims as written are directed to an isolated fragment of α3(IV) NC1 domain (or a composition comprising a fragment) having a **specific, recited amino acid sequence as set forth in SEQ ID NO:10**. As demonstrated in the examples of the specification, the inventor has discovered that this particular amino acid sequence contains the binding site for αvβ3 integrin, as well as the disclosed biological activities, including the ability to inhibit proliferation of tumor cells. **The claims as written do <u>not</u> include structural changes or modifications, and thus all non-Goodpasture fragments falling within the scope of the claims will have the recited activity.** No additional experimentation is required to

practice the claimed invention. Thus, Applicant respectfully requests reconsideration and withdrawal of the rejection.

The Examiner further states that it is uncertain "whether or not the claimed composition would *function* to inhibit proliferation of tumor cells in vivo," and that the specification does not provide "evidence which is reasonably predictive that the claimed pharmaceutical composition[s] are *effective for in vivo use,*" nor does it describe "*how to effectively use* the pharmaceutical composition as claimed" (Office Action, page 4, lines 8-12; emphasis added). Applicant respectfully traverses this rejection.

Applicant respectfully submits that the operability of the claimed non-Goodpasture fragments of α3(IV) NC1 domain is not at issue. The examples show that the non-Goodpasture fragment of α3(IV) NC1 domain having amino acid residues 185-203 and 181-244 of SEQ ID NO:10 (claims 1 and 9, respectively) have the ability to bind $\alpha_V\beta_3$ integrin and inhibit proliferation of tumor cells. It is well established law that if a compound itself is shown to have the disclosed activity (i.e., is operative or enabled), then compositions comprising the compound are similarly enabled. For example, in *In re Bundy*, 209 U.S.P.Q. 48, 51-21 (CCPA 1981), the court ruled that applicant's disclosure was sufficient to enable one skilled in the art to use the claimed analogs of naturally occurring prostaglandins even though the specification lacked any examples of specific dosages, because the specification taught that the novel prostaglandins had certain pharmacological properties and possessed activity similar to known prostaglandins. In the present case, not only does the specification provide evidence that the disclosed non-Goodpasture fragments have certain pharmacological properties, but it also (unlike the specification in *Bundy*) provides specific dosages and protocols for using compositions comprising the fragments (see, e.g., page 67, line 8, through page 70, line 22). Thus, Applicant respectfully submits that the specification provides enabling support for claims 1-4 and 9.

The Examiner then addresses the unpredictability of adhesion-based therapy, citing *Edgington Biotechnology* (1992) 10:383-389, and particularly page 386, column 3, paragraph 4. Applicant points out that the cited reference, published in *1992*, is not an accurate representation of the state of the art at the time the present application was filed (April *2000*). Moreover, the

present claims are directed to isolated fragments of α3(IV) NC1 domain having demonstrated biological activity and compositions comprising these fragments, not methods for treating adhesion-based disorders based on generalized principles, as discussed in the Edgington reference. Thus, Applicant submits that the Edgington reference is irrelevant to the issue of enablement of the present invention.

The Examiner also cites Kogan et al., *J. Biol. Chem.* (1995) as evidence that a "single amino acid can determine the ligand specificity of a selectin and the unpredictable nature of amino acid alterations in adhesion/binding activity" (Office Action, page 4, lines 23-25). As discussed above, **none of claims 1-4 or 9 recite fragments of α3(IV) NC1 domain comprising structural changes or modifications**, but rather are directed to specific, recited amino acid sequences of SEQ ID NO:10. Thus, Applicant submits that the Kogan et al. reference is also irrelevant to the issue of enablement of the present invention.

Finally, the Examiner concludes that "[i]n view of the quantity of experimentation necessary, the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention." However, as discussed in detail above, the claims as currently pending do not include mutants or variants of the fragments of α3(IV) NC1 domain, but rather are limited to specific amino acid sequences as set forth in SEQ ID NO:10. Such fragments have demonstrated biological activity, as shown in the examples. Moreover, the references cited by the Examiner as evidence of unpredictability and the state of the art do not support the proposition for which they were cited. The claimed invention is highly predictable and no additional experimentation is necessary. Finally, contrary to the Examiner's assertion, the instant application includes numerous working examples (36 to be exact) demonstrating the biological activity of the claimed fragments of α3(IV) NC1 domain.

For all of the foregoing reasons, Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 1-4 and 9 under 35 U.S.C. § 112, first paragraph.

Priority Claims

The Office Action reiterates statements from previous office actions, which state that the priority date of claims 1-3 is June 17, 1999, the filing date of U.S. App. No. 09/335,224, and that the priority date of claims 4 and 9 is April 4, 2000, the filing date of the present application.

As the Examiner has correctly pointed out (see Office Action, page 5, lines 14-19), to comply with the written description requirement of 35 U.S.C. § 112, first paragraph, and to be entitled to an earlier priority date or filing date under 35 U.S.C. §§ 119, 120, or 365(c), each claim limitation must be expressly, implicitly, or inherently supported in the originally filed disclosure (see also MPEP § 2163). Applicant respectfully submits that the claims as currently pending are implicitly or inherently supported in the earlier filed applications. U.S. App. No. 09/335,224 has an identical counterpart International Application, which published as WO 99/65940. One of ordinary skill, upon reading that disclosure, would have all of the information needed to isolate and assay additional anti-angiogenic fragments, including those disclosed in the present application. Moreover, according to the Examiner's reasoning, anyone can use the teachings of WO 99/65940 to isolate anti-angiogenic fragments. Thus, according to the Examiner's own logic, the fragments of the present invention are inherently supported by the previous filings. If that were not the case, then one of skill in the art, based on the teachings of WO 99/65940, could not arrive at the claimed invention.

Applicant therefore respectfully requests that the refusal of priority on these grounds be reconsidered and withdrawn.

Claim Rejections Under 35 U.S.C. § 102

Claims 1-4 are rejected under 35 U.S.C. § 102(b) as being anticipated by Kalluri et al., *J. Biol. Chem.* (1996) 271(15):9062-9068. The Office Action states that Kalluri et al. teach a composition comprising a non-Goodpasture fragment of α3(IV) NC1 domain as recited in the claims 1-4. The Office Action further states that the composition comprises serum, which "is considered to be a pharmaceutically-acceptable carrier" (page 7, line 4), and thus "the reference product is the same as the claimed product" (page 7, lines 11-12). Applicant respectfully points out that the cited Kalluri reference, which is the inventor's own work, does not disclose the

composition of claims 1-4. Specifically, nowhere in that reference is there any teaching or suggestion of combining an isolated non-Goodpasture fragment with a pharmaceutically acceptable carrier, as required by amended claim 1. Rather, the cited reference describes inhibition ELISA experiments using α3(IV) NC1 mutants in serum. Applicant respectfully submits that serum is not considered a pharmaceutically acceptable carrier. Serum is known to carry a variety of potentially fatal viruses and prions, including viruses such as Hepatitis C, HIV, etc., and many other known and/or as of yet unidentified pathogens. Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 1-3 are rejected under 35 U.S.C. § 102(b) as being anticipated by Han et al., *J. Biol. Chem.* (1997) 272(33):20395-20401. The Office Action states that Han et al. teach a composition comprising a non-Goodpasture fragment of α3(IV) NC1 domain in coating buffer (0.1 M Tris-HCL buffer, pH 7.5), "which is considered a pharmaceutically-acceptable carrier," and thus "[t]he reference teachings anticipate the claimed invention" (Office Action, page 7, lines 24-32). Applicant respectfully traverses this rejection. Nowhere in the cited reference is there any teaching or suggestion of combining an isolated non-Goodpasture fragment with a pharmaceutically acceptable carrier, as required by independent claim 1. Rather, the passage cited by the Examiner teaches an attachment assay wherein synthetic peptides are dissolved in conditioned medium, then added to wells of a 24-well plastic plate coated with the coating buffer. Applicant submits that conditioned medium is not considered a pharmaceutically acceptable carrier. Reconsideration and withdrawal of the rejection is respectfully requested.

Finally, Claims 1-4 are rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,973,120. The Office Action states that the `120 patent teaches a composition a non-Goodpasture fragment of human α3(IV) NC1 domain and "GP serum," which the Examiner apparently believes is a pharmaceutically-acceptable carrier (page 8, lines 5-9). Thus, the Examiner concludes that "[t]he reference teachings anticipate the claimed invention" (page 8, line 27). Applicant respectfully traverses this rejection. Nowhere in this reference is there any teaching or suggestion of combining an isolated non-Goodpasture fragment with a pharmaceutically acceptable carrier, as required by Applicant's claims. Rather, the cited reference describes inhibition ELISA experiments using antisera from two Goodpasture (GP)

patients. Applicant respectfully submits that serum from a GP patient, or any human or animal for that matter, is not considered a pharmaceutically acceptable carrier. Sera are known to carry a variety of potentially fatal viruses and prions, including viruses such as Hepatitis C, HIV, etc., and many other known and/or as of yet unidentified pathogens.

For all of the foregoing reasons, none of the references cited by the Examiner anticipate the subject matter of claims 1-4 and 9. Thus, Applicant respectfully requests reconsideration and withdrawal of the rejections under 35 U.S.C. § 102(b).

Applicant submits that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicant's attorney would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney of record.

Respectfully submitted,

Date: January 7, 2004

Barbara A. Gyure

Name: Barbara A. Gyure
Registration No.: 34,614
Palmer & Dodge LLP
111 Huntington Avenue
Boston, MA 02199-7613
Tel. (617) 239-0100